DEPARTMENT OF HEALTH

REPORT OF THE GENETICS RESEARCH ADVISORY GROUP

A First Report to the NHS Central Research and Development Committee on the new genetics

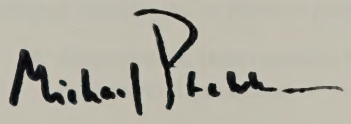
FOREWORD

A series of appraisals of growth areas in science and technology has been commissioned by the NHS Research and Development Programme. The purpose is to obtain a clearer view of the likely implications of major scientific discoveries for the NHS. This report is the first of two studies which have explored recent advances in genetics and their potential contribution to human health.

Developments in genetics are moving fast. This first report, which was presented to the Central Research and Development Committee last year, describes advances in the field of inherited disorders and indicates the wider prospects likely to emerge as the genetic components of common diseases become better known. Some evaluative studies of screening procedures and counselling techniques have already been commissioned following this report.

The second report, written later, has been able to build on and complement the earlier study. It describes how recent work on the genetics of common diseases is changing our understanding of the nature of these disorders, offering exciting new possibilities for diagnosis, prevention and treatment. Taken together the two studies clarify the opportunities provided by advances in basic science, and will link these developments to NHS R&D and to clinical practice for the benefit of the NHS and its patients.

The challenges identified in these two reports illustrate the approach identified in the White Paper *Realising our Potential*, and taken forward in the recent Technology Foresight Exercise. The report of this exercise, published in May 1995, emphasises the wealth creation aspects of science and technology and also its relevance to the quality of life. Advances in genetics offer the prospect of considerable gain not only for the NHS but also for the British pharmaceutical and health care industries, with attendant benefits of employment, exports and growth in national income. The contribution these two reports make to the NHS and to the wider endeavour set out in the *Technology Foresight Report* are welcome.



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SUMMARY

The development of new techniques for locating and identifying human genes, identifying gene products, and analysing the functions and interactions of those gene products is opening up unprecedented opportunities for rapid advances in our understanding of human biology and disease. These advances are already having a direct impact on virtually all areas of medical and surgical practice by facilitating:

- better tests to detect carriers of gene variants which render either them or their offspring particularly liable to certain diseases;
- the definition of the genetic components of common disorders, and their underlying pathophysiology;
- a clearer understanding of disorders at a biochemical level;
- preventive medicine through screening for genes which predispose to certain diseases.

Currently, the impact of these advances is on inherited diseases such as cystic fibrosis, muscular dystrophy, haemophilia, Huntington's disease, thalassaemia, myotonic dystrophy and Fragile X disease. In the future progress is likely to be in relation to more common disorders resulting from genetic/environmental interactions, such as diabetes, hypertension, asthma, coronary artery disease and several forms of cancer.

New therapies will be developed because our improved understanding of diseases enables a more rational exploration of pharmacotherapeutics, and because gene transfer (gene therapy) is becoming possible.

The NHS, both in terms of service commitments and of its R&D policy, needs to remain well informed about the potential of these advances, and to develop mechanisms for evaluating new approaches to diagnosis and therapy. The most important and promising advances must be developed rapidly and evaluated properly before being put into practice. It is important to avoid:

- Unevaluated interventions being put into widespread practice, due to medical, public or commercial pressures;
- Failure to benefit from major advances by withholding their practical application for an unduly long time while awaiting the results of evaluation. As scientific advances work through into medical practice, flexible and accessible prioritising systems will be as important as ensuring that adequate resources for R&D are available.

Specific points considered by the Group included:

Screening for Down syndrome. It is now well documented that the use of biochemical markers in maternal blood, in conjunction with maternal age, can identify a group of pregnancies at high risk of Down syndrome with greater efficiency than risk assessments made purely on the basis of maternal age. Specific ultrasound (U/S) markers of Down syndrome have also been described. Invasive and expensive diagnostic tests for Down syndrome, e.g. amniocentesis, can then be targeted at high risk groups. Further R&D is required to establish new markers, to extend screening into the first trimester of pregnancy, and to determine which combined testing protocols are most effective in practice. However, the full national application of current

techniques is likely to have a greater impact on the detection of Down syndrome pregnancies than new techniques under development. Further research is required into methods of conveying complex information effectively and efficiently to the patients as a prerequisite for informed decision-making.

New methods of chromosome analysis are being developed which obviate the need for time-consuming and expensive cell culture by enabling chromosome studies to be performed on non-dividing (interphase) cells. These may reach the stage of clinical application within the next few years. These tests are more specific which means that they will only detect the particular abnormalities for which they are designed, whereas conventional cytogenetic analysis is also capable of detecting spontaneously occurring and previously unsuspected chromosome rearrangements.

Other developments at the research stage involve novel methods of obtaining cells for prenatal cytogenetic analysis without sampling the fetus directly - either by extracting fetal cells from the maternal circulation, or by analysing trophoblast cells shed into the cervix.

Single gene disorders. New diagnostic tests are being developed for single gene disorders based on identifying specific genes and mutations within them. In general, the results of these tests within high risk families are sufficiently clear-cut to obviate extensive further evaluation. New technologies (particularly automated ones) for testing large numbers of samples for genetic mutations are under development and will require assessment. Such tests must be delivered within the context of genetic counselling, both before and after testing.

Further research is needed on the effectiveness of genetic counselling, and on different ways of delivering genetic information to patients.

For a few single gene disorders, particularly cystic fibrosis, new population screening methods are already available, or will become so. The motivation for screening may change over time, e.g. if newly developed therapies affect the prognosis of the disease, altering the demand for prenatal diagnosis.

Gene therapy. Gene therapy is already the subject of early clinical trials for a few diseases (e.g. some immunodeficiency disorders, cystic fibrosis, and some cancers), and will pose specific problems of manufacture, validation, and service delivery within the relatively near future. There may be a particular problem in determining who will pay for the development of gene therapies for rare disorders which are of little commercial interest.

Multifactorial disorders. The identification of genes involved in common disorders will open the way for both population-based screening programmes and the development of new therapies. Screening programmes may identify either those individuals for whom early intervention and treatment is advantageous, or those who require closer surveillance in future. Each screening programme, and each disease, will present a novel set of problems requiring specific evaluation. Deciding on R&D priorities in a field that could grow very rapidly may be difficult. Early involvement of both health economists and social scientists in a full evaluation of model population screening programmes (such as happened in recent evaluations of cystic fibrosis screening) might indicate how such evaluations could be conducted, and give some understanding of their complexity.

Genetic techniques in the laboratory. Genetic techniques are already in use in many areas of laboratory medicine, and their use is likely to increase dramatically. The technologies for

performing these tests, and proper assessment of their costs, benefits, and error rates, will need to be formally assessed before they are put into widespread practice.

Education. It is necessary to educate health professionals who have generally not been trained in genetics. The existing network of regional genetics centres provides a strong basis on which to build, and these centres will become increasingly important. They need to be strengthened now, and deployed as a major educational resource for training existing and future generations of health professionals, including primary health care teams, to whom much of the responsibility for genetic counselling will devolve in future.

Issues of public education in these new fields are also widely recognised as being very important.

Ethics. The ethical issues involved have not been considered separately in this report as they have already been thoroughly addressed elsewhere (1). Overall, the principles of genetic screening are similar to issues involved with screening in other fields (2), except with regard to the possibility of intervention. After genetic screening, interventions may include changes in lifestyle or reproductive decisions, as well as medical intervention in the conventional sense.

Recommendations. The group made a number of recommendations for the future attention of the NHS R & D Programme in the field of genetic medicine (see page 27).

1. INTRODUCTION

The last fifteen years have seen an explosion in our understanding of the molecular basis of medical disorders. New techniques have been developed which permit the identification and analysis of the physical and chemical structure of genes. Human gene function may be studied *in vitro* (i.e. outside the body), and by the construction of accurate (transgenic) animal models. Research initiatives such as the international Human Genome Mapping Project (HGMP) are producing important results, some with immediate implications for clinical practice.

The initial achievement of these programmes was the identification of genes responsible for inherited disorders such as muscular dystrophy, cystic fibrosis (CF) and familial adenomatous polyposis (FAP) (an inherited form of colon cancer). Most of the genes responsible for the more common inherited diseases have now been identified. Although the work is costly, time-consuming and difficult, it is clear that virtually all human genes will be isolated and characterised within the forseeable future. Since genes underlie all biological functions, understanding their mode of action will give new insights into the processes disrupted in disease, and will open new avenues for prevention and treatment.

Genetic disorders are a significant cause of poor health, and create considerable social and financial burdens for affected individuals, their families and society. They can be classified into:

a) ***chromosome anomalies*** (which are visible microscopically) – these are usually (>95%) not familial but arise as new mutational events in each affected individual.

b) ***single gene disorders*** – the common inherited conditions such as muscular dystrophy, thalassaemia and Huntington's disease, which are often familial.

c) ***multifactorial disorders*** – which have a more complex aetiology involving the interaction of several environmental and genetic factors. Many common adult disorders have a considerable genetic component, causing an increased susceptibility to disease (e.g. some cancers, coronary artery disease and diabetes).

Clinically significant advances are anticipated in all three categories.

Through clinical genetics, the medical profession has developed effective diagnostic and counselling strategies for chromosomal and single gene disorders. Wider knowledge of genes and their functions will provide further understanding of multifactorial disorders, and make genetic approaches important for virtually all areas of medical practice. New diagnostic techniques, new genetic and pharmacological therapies, and the possibility of screening large populations for predisposition to particular diseases, will present an array of formidable and exciting challenges to the health service.

The spectacular rate of scientific progress has been accompanied by the rapid clinical application of new skills and tests. For example, clinical testing has been made available within months of the discovery of the gene for diseases such as Duchenne muscular dystrophy, myotonic dystrophy, Fragile X mental retardation and Huntington's disease. These impressive advances are likely to continue, with the development of new genetic tests and gene therapies. Evaluating these advances and bringing them into clinical practice will be a major task for the NHS over the coming decades. The NHS must also act to ensure the full application of existing techniques of

proven efficacy and cost-effectiveness, the optimal organisation of genetic services, and the education of both the public and the medical profession.

The identification of abnormal genes in those suffering from genetic disorders has immediate application in facilitating testing for their close relatives, whose risks of inherited disease may be increased. Other applications under development include the testing of populations of "low risk" individuals (i.e. without a positive family history) for gene carrier status, and the development of gene therapies. Experience with the relatively uncommon inherited disorders will provide important information for use as genes involved in predisposition to common diseases are identified.

Advances in genetics have had a high public profile, generating considerable interest but leading to expectations and fears, some of which are unrealistic. These issues will have to be addressed as part of the implementation of new discoveries in the NHS. It is particularly important that the psychological and social impact of new forms of practice are included in any assessments of cost-effectiveness.

Much of the potential of genetics lies in its ability to predict biological effects which have not yet become clinically evident, but for which an effective intervention is (or may become) available. Therefore it is likely to have an impact on prevention as well as treatment. From a public health viewpoint, the possibility of improved health screening may have important future economic effects. In the immediate future, however, some tests may enable prediction only, in the absence of any effective treatment. Whether, and how, to deploy such tests requires careful consideration in each specific instance.

The following sections deal with issues of potential importance to the NHS under the various categories of genetic disorder. Separate chapters deal with gene therapy, the application of genetic techniques in laboratory medicine, and the organisation of genetic services.

2. ANTICIPATED ADVANCES IN RELATION TO DIFFERENT TYPES OF DISORDERS

2.1. Down syndrome and other disorders of chromosomes

Chromosomal abnormalities are caused by microscopically visible alterations of chromosome number or structure. They are untreatable and affect about 6 in every 1000 live births. Hundreds of different abnormalities have been described, of which Down syndrome is the best known. The effect depends on the chromosome involved, but surviving infants with chromosomal abnormalities are often mentally retarded, with multiple congenital malformations. Chromosome changes are also common in cancers, but in these conditions the abnormalities occur only in individual cancer cells, and are not part of the overall make-up of a person. Chromosome abnormalities are diagnosed in cultured cells from samples of blood, amniotic fluid, chorion villus, bone marrow and tumour tissue. There are specialised cytogenetic laboratories to undertake these analyses in each region in the UK.

2.1.1. Down syndrome and raised maternal age

The commonest chromosome abnormality in liveborn infants is Down syndrome (DS), or trisomy 21, where there is an extra chromosome 21 (1 in every 625 liveborn infants). A woman's risk of having a child with DS or some other chromosome abnormality increases with age, and health authorities have therefore offered prenatal diagnosis by amniocentesis at 16 weeks of pregnancy to women above 35-37 years. First trimester prenatal diagnosis is also possible (see 2.1.3).

2.1.2. Biochemical screening

Although the risk of DS increases rapidly after the age of 35 years, most DS babies are born to younger women (who have a lower risk but a higher birthrate), and these will not be detected using age-only selection. Research in the 1980s showed that information from a series of serum markers (including alpha-fetoprotein, unconjugated oestriol and human chorionic gonadotrophin) in pregnant women allows more accurate estimation of the risk of DS in individual pregnancies than calculations based on age alone (1, 2). Different combinations of biochemical markers are likely to improve cost-effectiveness, but the practical consequence of serum screening is to allow more specific targeting of amniocentesis, to include younger women found to be at high risk, increasing the proportion of DS pregnancies detected. Prior serum screening also provides the opportunity for older women found to be at lower risk to forego amniocentesis.

ESTIMATES OF THE INCREASED DETECTION RATE OF DS PREGNANCIES (1000 BIRTHS EXPECTED PER ANNUM IN THE ABSENCE OF SCREENING) IF SERUM SCREENING WERE IMPLEMENTED NATIONALLY

AGE SCREENING	Maximum reduction	300
	Best estimate	200*
SERUM SCREENING	Maximum reduction	600
	Best estimate	400*

* assuming two thirds amniocentesis uptake

Serum screening using a combination of biochemical markers is already widespread (1, 2), but not universally available.

A substantial majority of cases could be detected by widespread efficient application of existing screening tests.

Economic appraisals to determine 'the cost of finding the case' are complex, but early data suggest that the combined maternal age/serum marker approach is cost-effective. The evaluation of 'quality of life' factors remains problematical, and consideration needs to be given to the psychological and social consequences of screening. These include the stress of late termination of pregnancies after correct diagnosis, and the anxiety generated by false-positive and false-negative screening test results. All these factors need to be integrated into overall appraisals of screening programmes.

2.1.3. New first-trimester tests being developed

2.1.3.1. ***Screening tests***. Pregnancy screening in the first rather than the second trimester has obvious advantages. Ultrasound (U/S) scanning at 11-12 weeks gestation, for increased nuchal (neck skin) thickness as a marker of Down syndrome, is currently being evaluated, and preliminary data suggest that biochemical markers will be useful at this gestational age.

2.1.3.2. ***Diagnostic tests***. Chorion villus sampling (CVS) has a higher miscarriage rate than second trimester amniocentesis, and there is a risk of limb reduction defects when it is done before about 10 weeks gestation. First trimester amniocentesis is technically feasible, but its safety and efficacy relative to CVS and second trimester amniocentesis require adequate formal evaluation.

2.1.3.3. ***Non-invasive tests***. Non-invasive methods of sampling fetal cells would diminish the hazards of prenatal testing (mainly miscarriages). Two areas of current research are:

a) Retrieval of fetal cells from the maternal circulation (3).

b) Flushing of trophoblast cells from the cervix (4).

Both produce small numbers of non-dividing cells admixed with maternal cells, and sampling has been successful in early pre-clinical trials.

2.1.3.4. ***Chromosome tests***. Current chromosome diagnostic tests are based on analysis of mitotic (dividing) cells, but various methods using interphase (non-dividing) cells are being developed. Specific chromosomal identification is possible using FISH (Fluorescent In Situ Hybridisation), whereby visible, fluorescence-tagged chromosomal labels attach themselves to their targets. Another technique uses highly variable DNA markers to distinguish fetal from maternal cells, and to check for extra chromosome 21s in the fetus. These newer techniques are faster and less labour-intensive, but a screening test devised to detect only trisomy 21 (and perhaps trisomies 13 and 18) will miss other significant chromosomal abnormalities (e.g. translocations) which standard karyotyping would detect. As a result, some fetuses with chromosome abnormalities will not be identified by interphase prenatal diagnosis. All these techniques will require the establishment of their error rates, and large scale evaluation trials, including cost:benefit analysis, before they can move into clinical practice.

2.1.4. Conclusions – Down syndrome and other disorders of chromosomes

- A substantial majority of cases of Down syndrome could be detected by widespread application of existing screening tests, but more research is needed into various screening methods, including the timing and targeting of tests offered, as well as cost benefit analyses.
- Over the next decade, the biggest changes are likely to be a shift from second to first trimester screening, with diagnostic tests such as CVS and amniocentesis being targeted more selectively at high risk pregnancies.
- Further research is needed into newer diagnostic tests, including first-trimester amniocentesis, and non-invasive methods of sampling fetal cells.
- Less labour-intensive techniques of cytogenetic diagnosis may save time in the laboratory, but must be balanced against the lower detection rate for more unusual chromosomal abnormalities. This could present particularly difficult problems for evaluation.

2.2. Disorders caused almost entirely by single genetic factors ('Single gene disorders')

2.2.1. Genetic testing

Increasingly, genetic tests can establish whether a person, or a fetus, carries a particular abnormal gene. This information can predict whether a disorder will, or will not, develop, or whether a person is at a particularly high or low risk of having affected children. (Some common genetic disorders are listed in Table 1).

TABLE 1 FREQUENCY AND CHARACTERISTICS OF SOME COMMON GENETIC DISORDERS

NAME	INHERITANCE	FREQUENCY	CHARACTERISTICS
Down syndrome	Chromosomal (trisomy 21)	1 in 625 births	Mental retardation Congenital heart disease
Cystic fibrosis	Single gene (Autosomal recessive)	1 in 2000 births (1 in 25 carriers) among Caucasians	Progressive chest disease Malabsorption
Sickle cell disease	Single gene (Autosomal recessive)	1 in 400 births (1 in 10 carriers) among Afro-Caribbeans	Anaemia Sickle cell crises Strokes Organ infarcts
Huntington's disease	Single gene (Autosomal dominant)	1 in 10000	Premature dementia Abnormal movements
Duchenne muscular dystrophy	Single gene (X-linked)	1 in 4000 males	Progressive muscle weakness and wasting
Colon cancer	Single gene (Autosomal dominant e.g. familial adenomatous polyposis)	1 in 8000	Multiple polyps Early onset colon cancer
	Multifactorial	1 in 3000	Colon cancer

Sources

1. National Down Syndrome Register.
2. McKusick V.A. (1992) *Mendelian Inheritance in Man*, 10th ed. Baltimore, London: Johns Hopkins University Press.

Currently most genetic tests are done for people known by family history to have a comparatively high risk of carrying certain abnormal genes. For some disorders, such as cystic fibrosis (CF), Tay-Sachs disease, sickle cell anaemia and thalassaemia, it is technically possible to test large numbers of low risk people in the general population for carrier status (screening). Some long-established screening programmes already exist in particular population groups (Tay-Sachs disease in Ashkenazi Jews; thalassaemia in people from Mediterranean areas and the Far East; sickle cell trait in Afro-Caribbeans, etc.), based on biochemical or haematological assays. However, although these are well-researched areas, implementation of the relevant screening programmes within the NHS is imperfect, and prone to considerable local variation. One of the most highly developed screening programmes is the UK programme for thalassaemia, which involves haematologists and GPs as well as geneticists. The National Haemoglobin Reference Laboratory can screen for up to 200 different mutations, and has developed the expertise to study complex families (those with more than one mutation), in order to sort out what the clinical consequences of their different interactions might be. Whether the management of other genetic diseases, particularly the rarer and more complicated ones, would benefit from such centralised organisation, or whether regional laboratories will develop sufficient expertise to cover most genetic diseases, remains to be established.

2.2.1.1. Genetic testing protocols

Genetic testing in comparatively high risk situations is based on counselling before and after testing, intended to improve understanding and reduce unnecessary anxiety amongst those being screened. The amount of counselling necessary to achieve good results has not been established, nor is it known to what extent screening uptake is determined by the way in which the tests are offered. Further research is advisable to establish how large populations might be informed without such intensive counselling. Controlled studies comparing the effects of different genetic testing protocols should, wherever possible, include economic appraisals.

2.2.2. Cystic fibrosis

Mutations in the CF gene are present in about 1 in 25 of the indigenous UK population, and the birth incidence of this autosomal recessive disease is about 1 in 2000, making it the commonest disease in this category in the UK. Molecular tests enable the detection of more than 85% of CF mutations. Although more than 300 different mutations have been described, most are extremely rare, and the majority of CF carriers in the UK can be detected by screening for a few common mutations.

The most advanced proposals concerning genetic testing in the general UK population relate to CF (5-14). The issues to be considered include methods of offering the test, educational material provided, samples collected (e.g. blood, mouth wash), laboratory assays, and ways of communicating the result. The prospect of gene therapy in the foreseeable future could affect the demand for prior knowledge of CF carrier status, and detailed consideration needs to be given to the economic implications of CF carrier testing, both for its own sake and as a model for future genetic testing programmes.

2.2.2.1. Screening during pregnancy

CF screening has been piloted in antenatal clinics, in general practice, and in the

workplace. Antenatal CF screening is feasible, and about 200 of the 300 pregnancies at risk of resulting in the birth of a child with CF in the UK each year could be identified prenatally, at an annual cost of about £10 million (15). Traditionally, geneticists have focused on testing individuals, which also includes 'cascade' testing of relatives of identified carriers. However, a case has been made for collecting samples for DNA testing from both expectant parents instead, and only informing them of a positive result if both are found to be carriers – so-called 'couple screening' (13-16). The number of cases requiring post-test counselling is much smaller if a result is only considered 'positive' when both parents are found to be carriers, at which stage prenatal diagnosis can be offered. This approach may reduce anxiety (since the majority of carriers are not informed of their status), but it limits opportunities for cascade screening of relatives. Carrier couples who are only detected when a pregnancy is already under way also have fewer options.

TESTING FOR SINGLE GENES: FURTHER RESEARCH COULD ADDRESS:

- Who to screen? – Individual *vs* Couple
- Where to screen? – Hospitals
  – General practice
  – Antenatal clinics
  – Workplace
  – Schools
  – Community centres
- What support is needed? – Laboratory services
  – Counselling
- How to educate – Health professionals
  – General population

2.2.3. Problems caused by genetic testing

Testing for genetic disorders raises social and ethical problems such as stigmatisation, or discrimination against people found to carry an abnormal gene - e.g. by employers or insurance companies. It also raises cultural and religious issues (e.g. the acceptability of termination of pregnancy), and has psychological implications (studies are evaluating anxiety levels in newly identified CF carriers, and the extent to which individuals understand and retain the information they receive during counselling). These factors are also relevant to existing screening programmes for non-genetic disorders.

2.2.4. Preimplantation diagnosis

Preimplantation diagnosis (PID) involves genetic tests on one or two cells taken from an IVF (*in vitro* fertilisation) embryo. Only those embryos with normal genes are then chosen for implantation in the uterus. It is currently a research technique: to date, a few conceptuses at risk of lethal X-linked diseases have been successfully sexed prior to implantation, and homozygotes for the CF gene have been detected at this stage. The safety and accuracy of PID techniques require validation before they are put into widespread practice, and arrangements should be made for long-term follow-up of mothers and children, including psychological evaluation. The

technique is of potential value to a minority of prospective parents at high genetic risk who find pre-natal testing unacceptable because they will not consider termination of pregnancy, or those who have already had several terminations. For these couples, PID may offer the only hope of having a healthy child, and some couples are already deferring pregnancy until PID is more widely available.

2.2.5. Conclusions – Disorders caused almost entirely by single genetic factors

- Various models for genetic testing exist, and their relative merits require further assessment and evaluation, especially in low risk populations. Such assessments should include evaluation of ethical, psychological and economic considerations. Different programmes will be appropriate for different diseases and different social groups.
- Each disorder must be considered on its own merits. CF is one of the best-researched models to date: results from demonstration projects have confirmed the feasibility of screening for this disease despite the complexities of screening for a condition for which there is no universal test, variable carrier detection rates in different ethnic groups, an unpredictable clinical course – and there is now the emerging possibility of gene therapy.
- The level of counselling required in relation to different modes of genetic testing is unknown.
- Problems caused by genetic testing including the possibility of stigmatisation, discrimination (by employers or insurance companies), and the acceptability of termination of pregnancy must be considered for all diseases for which screening is offered.
- Consideration must be given to the extent of validation required before PID can be provided as a service, particularly in relation to the length of follow-up of children born after PID.

2.3. Diseases caused by an interaction between genetic and environmental factors

Some diseases are caused by the interaction of several genetic and environmental factors, and are called 'multifactorial'. Relatives of an affected person will have an increased disease liability compared with the general population, and this leads to familial clustering, but in a way which is generally distinguishable from single gene inheritance.

It is estimated that 80-85% of the aetiology of schizophrenia and asthma is accounted for by genetic factors, about 60% in coronary artery disease, and about 35% in peptic ulceration (17). Increasingly it is evident that there is a significant genetic component in the aetiology of a number of diseases – for example, colon and breast cancer, diabetes and Alzheimer's disease. These discoveries offer the prospect of identifying at-risk individuals, and instituting preventative measures e.g. educating them about life-style changes to diminish environmentally induced expression of a disease, or monitoring for early diagnosis and treatment.

UNCERTAINTIES REGARDING SCREENING PROGRAMMES FOR PREDISPOSITION GENES IN MULTIFACTORIAL DISORDERS

- Unknown number of genes involved in each disease
- Attributable risk of each gene uncertain
- Efficacy & cost-effectiveness of different screening programmes not established

The debate on widespread population screening for predisposition to common multifactorial diseases has barely begun. The cost benefit ratios of various protocols will need evaluating, and contributions from clinicians, scientists, epidemiologists, health economists, and the population being screened are all essential. Much of this new clinical and preventative medicine is likely to take place in primary care or in the community.

2.3.1. Common diseases with a significant genetic component

In dissecting the aetiology of several common multifactorial disorders, e.g. coronary artery disease and several cancers, various single gene disorders are being identified. It is probable that genetic components will be documented in other common diseases in the near future, and this will open up opportunities for an increased understanding of the underlying biology, and the design of new therapies, as well as the possibility of defining high risk populations.

2.3.1.1. ***Myocardial infarction***. Several abnormalities of cholesterol metabolism which carry a high risk of coronary artery disease are controlled by single genes, and screening for some of these (e.g. type II familial hypercholesterolaemia, type I hyperchylomicronaemia) is already possible. A deletion polymorphism in the angiotensin-converting enzyme (ACE) gene is also associated with higher levels of circulating ACE and an increased risk of myocardial infarction, raising the possibility of pre-symptomatic pharmacological intervention (18).

2.3.1.2. ***Cancer***. Some uncommon familial cancer syndromes are caused by inherited single gene defects, but most cancers are probably the result of a combination of genetic and environmental factors.

For example, approximately 5% of cases of breast cancer are familial, and in about half of these, the susceptibility to breast or ovarian cancer may be due to mutations in the BRCA1 gene. In people who are born carriers of a mutant BRCA1 gene, the risk of breast cancer may be up to 89% by 60 years of age (19). Individuals at high risk might be candidates for prophylactic hormonal therapies or surgery, or may be targeted for frequent screening e.g. by mammography or breast ultrasound. Specific strategies would require formal evaluation. Although it seems likely that screening relatives of patients found to have a mutant BRCA1 gene will be worth while, the value of population-based screening for the BRCA1 gene will need further evaluation. It will depend largely on the prevalence of the gene in the general population, the attributable risk of breast and ovarian cancer associated with specific mutations, and the effectiveness of cancer-prevention strategies. Large, carefully controlled clinical research programmes in this area will be urgently required within the next year or two. There is also evidence that carriers of the ataxia telangiectasia gene may also be predisposed to early-onset breast cancer (20), but these patients are possibly hypersensitive to ionising radiation, so that mammography may be contraindicated for them.

BREAST CANCER: FUTURE RESEARCH COULD ADDRESS:

- Evaluation of population-based screening for single genes
- Efficacy of targeted screening in younger women
- Cost:benefit implications of widespread genetic screening

Most colon cancer is sporadic, but about 1% of cases occur in individuals with familial adenomatous polyposis (FAP) due to mutations in the adenomatous polyposis coli (APC) gene for which genetic testing is available. Other autosomal dominant inherited genetic abnormalities associated with an increased risk of colorectal cancer are being identified, and may account for 5% (or more) of all cases, especially those diagnosed at a young age (21). Individuals found to be at risk of developing colon cancer can be screened regularly by colonoscopy, and prophylactic surgery offered if multiple colonic adenomata are found. In some such families there is also an increased risk of extra-colonic cancers, particularly endometrial carcinoma, and screening for these may be of benefit to close relatives of index cases. The genes responsible for increased susceptibility to colorectal and other cancers are beginning to be identified. Tests for mutations in these genes may be available soon.

It has been suggested that tests for oncogene abnormalities (p53 gene) on stool samples may be an effective method of screening for pre-malignant change, but this gene too awaits further evaluation.

Women at high risk of developing ovarian cancer may elect to have their ovaries removed once they have completed their families as conventional treatment for this particular cancer has a poor success rate.

Risk estimates for clinical disease may have to be based on tests at several different gene loci.

2.3.1.3. ***Hypertension, pre-eclampsia in pregnancy, and stroke.*** Initial success in mapping genes associated with hypertension in rats is assisting the identification of candidate genes in humans (22).

2.3.1.4. ***Diabetes.*** Both juvenile-onset (Type 1, or insulin-dependent) and maturity-onset (Type 2, or non-insulin-dependent) diabetes have a recognised genetic component. Extensive studies have identified several gene loci involved in a mouse model of Type 1 diabetes (23). Specific human loci shown to be associated with diabetes in some families include the insulin receptor gene on chromosome 11, and genes within the human major histocompatibility complex on chromosome 6 (24). Identifying people at risk of developing diabetes may be worthwhile as good early control of blood glucose levels reduces the likelihood of complications.

2.3.1.5. ***Asthma.*** The familial tendency to asthma has been recognised for many years. The identification of a locus for atopy on chromosome 11q could be a prelude to the isolation of specific genes, possibly related to IgE response (25), but awaits further research.

2.3.1.6. ***Motor Neurone Disease (MND).*** The majority of cases of MND are not genetic. It has, however, been shown that a rare disorder called familial amyotrophic lateral

sclerosis (FALS) is caused by the absence of a specific enzyme (superoxide dismutase). This is an excellent example of how a genetic observation provides insight into the biological processes involved. The enzyme, which is involved in protecting cells from chemical damage, is absent from birth in patients with FALS, and yet progressive motor nerve deterioration only becomes apparent in adult life. This leads to speculation that control might be achievable by dietary or pharmacological manipulation.

2.3.1.7. ***Alzheimer's Disease.*** A genetic marker (Apolipoprotein E polymorphism) associated with a predisposition to late-onset Alzheimer's disease has been identified recently (26), and individuals with a substantially increased risk of developing this dementing illness could be identified. In the absence of an effective intervention or a clear understanding of the biochemical basis of this association, however, there is no indication for instituting screening programmes. There are also likely to be other genes involved in a series of complex interactions of which, as yet, we have little understanding.

2.3.2. Pharmaceutical developments

The discovery of new gene families involved in disease processes is likely to provide new targets for drug intervention, and pharmacological approaches to treatment will attempt to alter the underlying pathophysiology, rather than merely treat the symptoms of the disease.

2.3.3. Conclusions – Multifactorial diseases

- Progress in mapping and cloning disease genes will lead to the development, over the next decade, of genetic tests which could be used to identify predispositions to a range of common disorders, although initially only a small proportion of the total risk is likely to be identifiable.
- In each area of research it will be necessary to establish the relationship of particular genetic changes to the clinical disorder. These scientific discoveries may be useful to the NHS in several ways:

  a) Understanding some of the underlying biochemistry of the disease may assist in developing new therapies;

  b) Screening to identify those at high risk of the disease may allow targeted effective prevention or early management.

  Each strategy, for each disease, will present new issues in R&D. There is likely to be an avalanche of new medical strategies put forward for evaluation. The costs, in time and money, of evaluating them may be very substantial. It would be undesirable, however, either to allow the widespread introduction of unevaluated protocols, or to neglect potentially useful technologies.

  Mechanisms will need to be in place to establish priorities for the evaluation of promising advances. This would be assisted by work towards a coherent policy on the objectives and limitations of genetic screening. Unless the ground is well prepared, initial excitement at the prospect of new ways of combatting disease could turn to disappointment and frustration at the failure to translate scientific advances into validated medical strategies.

3. GENE THERAPY

The introduction of a normal gene into a patient with a defective or absent gene is an obvious application of genetic technology to human disease. Genes can be isolated and inserted into the patient's cells, but many challenges remain. The relative advantages of a variety of delivery systems, including viruses, liposomes, and receptor-mediated uptake, are being actively researched. Gene therapy for recessive disorders in which there is a deficiency of an enzyme, or other proteins, is technically reasonably straightforward, and therapeutic trials are under way. Corrective gene therapy, which would require the replacement of a mutant gene with a normal sequence, is still a long way off.

The appropriate targeting of the normal gene at the relevant organ(s) is intrinsically difficult for all genetic diseases except those which are caused purely by defects in cells in the bone marrow (e.g. immunodeficiencies). Concerns about transferring genes into foreign cells relate to the safety of these procedures, as there is potential for accidents to occur if inserted genes end up in the wrong place and, perhaps, interfere with the function of another critical gene, or activate an oncogene. Oncogene activation is extremely unlikely with any of the protocols currently being considered, however, as it is known from animal model studies that high level viral replication is required to get insertional activation. Prerequisites for human gene therapy have been established, and candidate diseases identified (1). Early clinical trials have already begun. The Medical Research Council has a major initiative on the genetic approach to human health, which is directing substantial research funds into developing gene therapy in the UK.

The use of molecular genetic techniques to devise chemotherapeutic agents which can be targeted specifically at tumour cells is probably the area which will develop most rapidly over the next five years. These agents will be administered by oncologists, as an extension of their range of chemotherapeutic drugs, and can be regarded more as a logical development of existing pharmacology than something completely new.

Despite all its difficulties, safe and effective gene therapy may become available over the next five to ten years for a number of diseases, including some immune deficiencies, cystic fibrosis (CF), some cancers, haemophilia, and a rare form of atherosclerosis caused by hypercholesterolaemia. There is a need to consider commercial implications of this potentially rapid transfer of technology from research into clinical practice.

REQUIREMENTS BEFORE WIDESPREAD IMPLEMENTATION OF GENE THERAPY IS POSSIBLE:

- Has safety been established?
- Is treatment possible?
- Is effectiveness proven?

3.1. Cystic fibrosis

It is hard to predict timescales, but the enormous effort going into the development of gene therapy for CF means that it will be surprising if protocols with some demonstrable benefit for patients are not available within five years, leading to considerable political pressure for their adoption into practice. In response to such pressure, the United States government has set up nine centres (at a cost of between $2.25 and $4 million dollars each per year) for five years, to study gene therapy in CF. The NHS must be ready to evaluate new therapies rapidly, and to deliver any therapy that has been shown to be effective and cost-effective in the face of forceful demands for early application from patients' families, and from those trying to recoup the financial cost of developing such therapies.

The initial phase of clinical trials, lasting one to two years, will concentrate on whether the gene therapy reaches the relevant organs, is stable, and works. Delivery systems based on liposomes (lipofection) may have potential, but it remains to be seen whether there will be a fall-off in effectiveness as a result of antibody production, or any side effects as a result of the host's immune response. Longer-term follow-up, lasting decades, will be necessary in order to identify any insertional mutagenesis, oncogene activation, or inadvertent transmission of unwanted material. The possibility of germline effects will only be established when future generations have also been reviewed. The MRC Gene Therapy Co-ordinating Committee has recommended that details of all patients receiving gene therapy, and those delivering it, should be noted, so that problems further down the line may be recognised easily. This will have financial and organisational implications.

In the longer term, the costs of clinical trials in some situations may be offset by the potential benefits of the development of successful therapies (including reductions in the financial cost of long-term care without gene therapy and in relieving the burden of the disease). Money spent on trials should result in better care, and fewer resources wasted on unevaluated treatments. If straightforward lipofection works in humans as it does in model systems, clinical trials would yield useful Phase 1 data within six months, and a large Phase 3 trial would be under way within five years. One practical problem to be overcome will be the establishment of laboratories to manufacture virus and liposome vectors, as academic laboratories will not be able to manufacture these to sufficiently rigorous clinical standards.

3.2. Cancer

Cancer treatment is likely to benefit considerably from the application of gene therapy techniques. Indeed, many protocols already exist, either in clinics or awaiting approval. These either seek to deliver toxin genes to the tumours, or to vaccinate the patient with genes for cytokines so as to induce host-immune responses to the tumour. Many of these protocols target diseases for which there is currently no effective therapy (e.g. malignant melanoma and renal cell carcinoma), and so any success will lead immediately to demands for widespread application. The seriousness of cancer means that it is inevitable that treatments may go ahead in patients without the rigorous testing in animal models which applies to many other diseases. In the longer term, strategies designed to deliver functional copies of tumour suppressor genes to

the organs of patients with cancer predisposition syndromes may be successful. Similarly, it may be possible to block expression of dominant oncogenes (such as the RET oncogene in multiple endocrine neoplasia). Although none of these approaches has been shown to be efficacious, it seems very unlikely that there will not be some successful outcomes among the many different avenues of cancer therapy being explored.

3.3. Haemophilia

Successful protocols for the treatment of haemophilia are likely to be developed within two or three years – Factor IX deficiency will be treatable before Factor VIII deficiency, for technical reasons. There is considerable commercial interest in this area, and the work is facilitated by the availability of good animal models.

3.4. Immune deficiencies

These have been the target of several protocols: already some patients with adenosine deaminase (ADA) deficiency have been treated with impressive early results, and as the genes involved in other immune deficiencies are cloned, further opportunities for gene therapy will become available. These are likely to be exploited rapidly because of the comparative ease with which such treatment can be targeted at the bone marrow.

3.5. Coronary artery disease

Preliminary trials in several patients with familial hypercholesterolaemia secondary to LDL (low density lipoprotein) receptor deficiency look very encouraging (2). If other predisposing genes can be identified and are amenable to similar treatment, gene therapy for this common condition may well, in the long term, be the one which provides benefits for a large number of people.

SERVICE IMPLICATIONS OF GENE THERAPY

- Prerequisites for human gene therapy have been established and candidate diseases identified.
- Early clinical trials have begun.
- Effective gene therapy may become available over the next 5 – 10 years.
- There is commercial interest in developing therapies for common disorders, but probably not for rare diseases.
- Some diseases which are likely to respond to gene therapy do not have any effective therapy currently e.g. malignant melanoma.

The fact that most research and development (R&D) work is being done in the USA, and therefore involves US patenting of genes and genetic technologies, may pose financial and administrative problems.

3.6. Conclusions

- If lipofection works for CF, and if the vaccination approach works for melanoma and renal cell carcinoma, clinical trials and subsequent implementation of gene therapy will proceed rapidly over the next decade.
- Large trials may be required to evaluate potential therapies. Long term follow-up will be required to assess safety issues and economic evaluation will be important. There will also be a time delay involved in enrolling suitable patients.
- There are undoubtedly considerable technical problems to be overcome, but in theory gene therapy should work, and commercial organisations are already investing huge amounts of money in R&D.
- Overall, the implementation of possible gene therapies needs immediate consideration, so that logistical and financial problems can be addressed. In several diseases, the total number of patients eligible for treatment may be too small to interest conventional pharmaceutical companies, but the cost to the NHS of not offering these patients gene therapy would be high. There may be a particular problem in determining who will pay for the development of new gene therapies for rare disorders which are of little commercial interest.

4. GENETIC TECHNIQUES AND LABORATORY SERVICES

The techniques which underpin current genetics research are also having beneficial effects in areas which are not directly related to genetics. The universal applicability of the new technologies being developed has already been demonstrated in several fields – e.g. histopathology, immunology and microbiology – and many laboratories have adopted new genetic tests to replace existing techniques. It is likely that molecular techniques will continue to have increasingly broad applications throughout the NHS, resulting in improved accuracy, faster results, and ultimately, in better treatment for patients.

4.1. Histopathology

For many human cancers several of the genetic events responsible for tumorigenesis have been identified. The detection of tumour-specific mutations in oncogenes and tumour suppressor genes can be used to characterise tissue samples, and to predict prognosis and the likely response to conventional therapy, which may influence the management of patients considerably. These changes need evaluation, including consideration of the implications of replacing subjective expert opinions with more objective molecular tests.

The monoclonal proliferation of lymphocytes in localised lymphoma or in the bone marrow can be diagnosed by Southern blot or PCR (polymerase chain reaction), enabling the detection of minimal residual disease after therapy.

The identification of genes which are expressed in a lineage-specific manner has implications for differential diagnosis. The expression of MYOD1 by rhabdomyosarcomas, for instance, distinguishes these tumours from primitive neuroectodermal tumours, which are treated very differently.

The detection of point mutations in RAS oncogenes, using PCR technology, could help in the diagnosis of pancreatic and lung cancers in cytology specimens, and could be used to screen faeces or urine for cells shed from colorectal or bladder tumours, respectively. As with most cancers, early diagnosis may considerably improve the long-term prognosis.

In bone pathology, where diagnosis on morphological grounds alone is often difficult, the detection of mutations in tumour suppressor genes such as TP53 and Rb1 can be used to differentiate neoplastic from non-neoplastic lesions (e.g. an osteogenic sarcoma from an aneurysmal bone cyst), influencing decisions about amputation.

The ability to predict responses to a particular form of therapy, at first presentation, would also be of great value. For example, over-expression of the ERB-B2 oncogene in breast cancer is associated with short survival and poor response to chemotherapy and endocrine therapy, so that these patients could be spared distressing treatment which is unlikely to provide any benefit (1).

Many of the new molecular tests which may have considerable potential for improving the clinical care of patients are currently only available on a research basis in a small number of laboratories (mainly funded by the Research Councils and charities). Integration of molecular tests into NHS practice will require a significant investment after formal evaluation of their relative usefulness. It is likely that they will prove highly cost-effective because of subsequent improvements in the clinical management of patients.

4.2. Immunology

Genetic techniques allowing precise definition of tissue antigens are beginning to replace the use of serology and mixed lymphocyte cultures for tissue typing in transplantation. Furthermore, the development of recombinant antibodies and other molecules which recognise cell surface epitopes may allow *in vivo* (and *in vitro*) diagnosis, such as the use of E-selection imaging in rheumatoid arthritis (2), and ICAM1/VCAM1 for the early diagnosis of transplant rejection.

4.3. Microbiology/Infectious diseases

Laboratory diagnosis of several infectious diseases is being revolutionised by the advent of genetic characterisation. Formerly, the confirmation of tuberculosis required laborious, technically difficult culture of clinical specimens, taking some six weeks, whereas now PCR amplification of mycobacterial gene sequences enables detection within a few hours. Antibiotic-resistant strains of *Mycobacterium tuberculosis* represent a major public health problem, but with molecular techniques the genes conferring this phenotype are detectable at presentation, facilitating correct treatment choice.

Electron microscopy (EM) for viral particle detection is technically difficult, relatively insensitive and non-specific, and requires expensive equipment. Multiplex PCR using a panel of oligonucleotide primers for various candidate pathogens can be applied to all kinds of specimens, and is particularly useful for diarrhoeal diseases.

PCR detection of viral genes looks particularly useful for infections with the hepatitis B and hepatitis C viruses, and the human immunodeficiency virus (HIV), where cases may be missed in the early stages if ELISA (enzyme-linked immunosorbent assay) testing is relied on.

Plasmid profiling in order to identify bacterial strains when tracing outbreaks of disease has been in use for some years. Molecular techniques are rendering this more sophisticated, and widening the spectrum of organisms which can be identified.

GENETIC TECHNIQUES MAY LEAD TO:

- Improved accuracy
- Faster results
- Better patient care

4.4. Conclusions

- The large amounts of money being invested in the development of new molecular gene-studying techniques are producing dividends in several fields of diagnostic pathology.
- The detection of gene mutations can be used in diagnosis, and to predict prognosis and the likely response to treatment, influencing the management of patients.

5. DELIVERY OF GENETIC SERVICES IN THE NHS

5.1. Regional genetics centres

There are about 60 consultant clinical geneticists in the United Kingdom, based in some 20 regional genetics centres, with at least one in each NHS region. Clinical geneticists provide counselling for families with inherited diseases, working closely with genetic counsellors, laboratory staff and other clinicians. They provide specialist training, and undergraduate and postgraduate teaching. This is a strong, highly integrated service, which provides a sound foundation for the successful exploitation of future scientific advances.

Genetic counsellors also inform people about genetic tests, ensuring that they understand the results. Counselling is intended to be non-directive and non-coercive, allowing people to decide for themselves what use to make of the information, and supporting them in their decisions. There has been relatively little research in the UK on the process of genetic counselling, and no systematic evaluation of the relative merits of different modes of service delivery. The huge increase in the number of genetic tests available, and their increasing relevance to the health of many individuals, means that in the future genetic services are more likely to be offered outside the regional centres, for example in primary care, antenatal clinics and general medical outpatient departments.

5.2. National screening service

There is no adequately integrated public health screening service to oversee the application of national screening programmes, and existing services tend to be fragmented and patchy (1). Regions vary in their provision of screening programmes. The Chief Medical Officer (2) has recently highlighted the need to evaluate screening programmes before they are introduced into health services, and for adequate monitoring and review subsequently.

5.3. Genetic registers

Most regional genetics centres maintain genetic registers to facilitate the identification and regular follow-up of affected and at-risk individuals. Pre-pregnancy counselling and carrier detection is facilitated, so avoiding stressful and uneconomic attempts at defining carrier status during pregnancy. When new research findings result in more accurate diagnosis, more effective prevention, and improved management or treatment of disorders, appropriate patients can easily be identified and contacted. Genetic registers permit regular audit, and provide a resource for R&D. A well-maintained register requires a skilled curator.

5.4. Storage of medical records and pathological material (including DNA) for genetic tests

Medical records and biological samples (usually as banked DNA, Guthrie cards, or pathological specimens) from families with serious single gene disorders should be stored to meet future requirements e.g. molecular confirmation of diagnoses, presymptomatic or prenatal diagnosis, and carrier detection. The Guthrie card from a deceased affected infant may be the only source of DNA available, and inadequate storage of Guthrie cards compromises the future availability of genetic testing for relatives (3, 4). Technical matters relating to the optimal storage of Guthrie cards should be the subject of R&D in collaboration with regional genetics centres. Long-term storage is necessary because new knowledge is associated with new test procedures being developed, and stored material permits retrospective characterisation of genetic defects in unusual disorders. Establishing the correct diagnosis may permit carrier detection before pregnancy, avoiding the need for potentially harmful prenatal tests or the termination of normal pregnancies because of extreme parental anxiety. Relatives who can be shown not to have inherited an abnormal gene can subsequently be excluded from expensive and unnecessary clinical follow-up.

5.5. Genetic testing in general practice

Testing for the CF gene, and eventually other genes, could also be provided in general practice. Regional genetics centres and their laboratories could continue to provide expertise and advice, but much clinical and preventative work could take place in primary care settings. The primary health care team (PHCT) has often known the patient for some time, is aware of the family circumstances, and will see the couple at an early stage of pregnancy (5). Means of realising the full potential of PHCTs as first-line providers of genetic testing should be developed and evaluated further.

The expansion of testing for genetic disorders into the general population means that new methods of service delivery will need to be developed and evaluated. Other health care workers will need training in counselling skills, and laboratories capable of handling large numbers of samples will need to be developed.

5.6. Organisational issues for the NHS

If large-scale genetic testing is to be offered, the NHS faces a number of organisational and financial challenges. What structure will be needed to handle large numbers of samples, while maintaining scientific standards? What will the role of the regional genetics laboratories be? Most monogenic diseases are heterogeneous at the molecular level, i.e. many different mutations may underlie the same clinical disorder. This has important implications because different molecular interactions may produce different clinical pictures. In the field of thalassaemia, this has already been well worked out and a National Haemoglobin Reference Laboratory has been

established. Such knowledge is not available yet for many other monogenic diseases, however, and the complex molecular heterogeneity of many genetic diseases poses organisational problems for the NHS. Will every regional laboratory develop expertise in all the common monogenic disorders to deal with these problems? If not, will particular laboratories be designated in each field? If so, how will the NHS cope with the transport of material, arrange counselling, and so on? Can the commercial sector, which is already successfully involved in forensics, immigration and paternity testing, make a contribution? It is extremely important for the patients that the availability of a laboratory test is not separated from proper counselling and family studies, and genetic counsellors need to be able to liaise with laboratory staff for the proper interpretation of results. Genetic testing done without careful patient education and follow-up is potentially dangerous and must be avoided. Quality control, appropriate follow-up, and efficient audit of both laboratory and clinical components of any screening programme must be equally rigorous in the NHS and in the commercial sector.

There will be a need for a central mechanism to ensure the rational development of facilities to avoid costly overlap and duplication. Before any major screening programme can be introduced, health care professionals from a variety of disciplines will need to be trained. Continuous systematic public education programmes will be needed.

5.7. Non-NHS Funding

Most research is funded by a variety of governmental and charitable research funding organisations, which are independent of the NHS. NHS patients assist in this work, and may benefit subsequently as independently-funded research works through into clinical practice. The dependence on non-NHS and short-term funding may pose risks for the continuity of newly established genetic services, however.

5.8. Patents

The cost of molecular genetic tests may be affected by patents on the techniques, such as PCR, and on gene sequences used in the tests. Individual laboratories have little bargaining power, but a collective approach, in which, for example, negotiations with suppliers might be conducted on behalf of the laboratories by the NHS Executive, would strengthen their position.

5.9. Conclusions

- The network of regional genetics centres provides a focus of co-ordination and expert advice, and this will continue to be needed. Genetic counselling and testing may also be provided by other agencies, e.g. in primary care, and this extension of screening programmes needs to be evaluated.
- There needs to be a national screening structure to ensure that effective screening programmes are available to the public on an equitable, high quality basis.

- Genetic registers are a valuable resource for assisting screening programmes and ensuring the appropriate storage of medical records, DNA and pathological specimens.
- Adequate training of health professionals and the public will present a significant challenge in terms of staffing and resources.
- If new advances are to continue to be transferred effectively from research laboratories into the NHS, NHS scientists will need adequate safeguarded time for R&D, as part of their contractual obligations, in order to set up and evaluate new screening tests.
- There is a need to clarify and monitor the position regarding patents on genetic sequences.

RECOMMENDATIONS

1. Serum screening for Down syndrome in pregnancy

It is established that serum screening is an effective method of detecting Down syndrome in mid-pregnancy, and should replace screening using maternal age alone. Evaluation of the various combinations of established and new markers (serum and U/S) needs to continue. Informing women about screening, and providing appropriate counselling, is an essential part of screening, and requires ongoing research and development.

2. Screening for cystic fibrosis

Screening for cystic fibrosis has been shown to be feasible in pregnant and non-pregnant populations. Evaluation of the relative merits and efficacy of different approaches to screening should include psychological, social and economic outcomes.

3. Screening policy.

The interests of efficiency and equity indicate a need for some forum for developing national policy guidelines for implementation of genetic screening programmes, comparable with those that exist for cancer screening programmes, as an aid to purchasers of health care.

4. Counselling

Critical appraisal of the processes of genetic counselling, both in high risk families and in relation to cost-effective counselling in large-scale screening programmes, is needed to enable individuals and health care purchasers to obtain optimum benefit from these advances.

5. Early amniocentesis

A controlled trial to compare the safety and efficacy of early amniocentesis with conventional amniocentesis and CVS should be reconsidered.

6. Interphase cytogenetics

Techniques are improving rapidly, and judgements will be required soon as to whether new cytogenetic techniques involving non-dividing cells (interphase cytogenetics) should replace standard chromosomal analysis in certain circumstances (e.g. prenatal exclusion of Down syndrome). The possible advantages of interphase studies are that they may be cheaper and quicker to perform. A consequence that needs consideration is that some other chromosomal anomalies, which can only be detected by standard chromosomal analysis, will not be identified.

7. DNA analysis

Analysis of specific mutations will be increasingly important for both diagnostic testing and for screening of low risk populations. New technologies for detecting mutations in

specific segments of DNA are being developed, and will require evaluation as part of a health technology assessment programme.

8. Pathology laboratory techniques

Application of molecular genetic techniques to areas such as tumour pathology and microbiology is leading to new diagnostic tests - sometimes in the form of 'kits', and often linked to expensive dedicated laboratory apparatus. Health technology assessment in these areas should determine the clinical value, efficacy and cost-effectiveness of different methods, and so help laboratories to choose the best protocols.

9. Therapy involving genetic techniques

Substantial therapeutic advances are likely in some fields. Current research is still primarily at the scientific development stage. Health services research issues will arise, and, although not imminent, need to be planned for well in advance.

10. Screening for predisposition to multifactorial disease

A watching brief should be maintained in this area. 'Predisposition genes' are likely to be identified, but screening programmes will not be appropriate until far more is understood about the number of genes involved in each disease, the attributable risk of each gene, and the efficacy and cost-effectiveness of different screening programmes.

11. Public and professional education

In this very new and rapidly changing field, there is a need for continuing education of health professionals, including primary health care teams, so that the implications of recent advances are appreciated and conveyed appropriately to patients. The regional genetics centres have an important role to play here. Public education also presents continuing challenges. Methods of conveying information to the public require research and evaluation.

12. Further advice

The Advisory Group recommends that a differently constituted group, including representatives of the R&D community, health economists, social scientists, purchasers, providers, public health physicians and GPs, should now take this report forward, and keep this rapidly advancing field under review.

MEMBERSHIP OF THE GROUP

The Group which produced the report was chaired by Professor Martin Bobrow, and comprised Dr. Nicholas Lemoine, Professor Rodney Harris, Dr. Timothy Harris, Professor Stephen Holgate, Dr. Theresa Marteau, Professor Alexander Markham, Dr. Peter Rigby, and Professor Nicholas Wald. Dr. Frances Flinter was the scientific secretary.

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GLOSSARY OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
ADA	Adenosine deaminase
AID	Artificial insemination by donor
APC	Adenomatous polyposis coli
CF	Cystic Fibrosis
CVS	Chorion villus sample
DoH	Department of Health
DS	Down syndrome
ELISA	Enzyme-linked immunosorbent assay
EM	Electron microscopy
FALS	Familial amyotrophic lateral sclerosis
FAP	Familial adenomatous polyposis
GP	General practitioner
HGMP	Human Genome Mapping Project
HTA	Health technology assessment
ICAM1/VCAM1	Intercellular adhesion molecule figure 1; vascular cell adhesion molecule 1
IVF	*In vitro* fertilisation
LDL	Low density lipoprotein
MHC	Major histocompatibility complex
MND	Motor neurone disease
NHS	National Health Service
PCR	Polymerase chain reaction
PHCT	Primary health care team
PID	Preimplantation diagnosis
R&D	Research and Development
U/S	Ultrasound
WHO	World Health Organisation

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